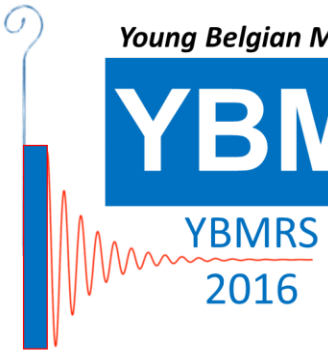

Young Belgian Magnetic Resonance Scientists

YBMRS 2016

15th edition

5th and 6th December 2016

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Kinetic studies of phosphoester hydrolysis promoted by a dimeric tetrazirconium(IV) Wells-Dawson polyoxometalate by NMR spectroscopy

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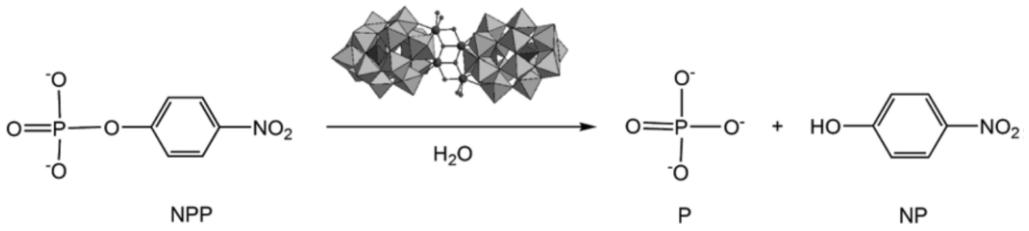
The detailed kinetic study of catalytic hydrolysis of a phosphoester bond in the DNA-model substrate 4-nitrophenyl phosphate (NPP) promoted by Zr^{IV}-substituted Wells-Dawson type polyoxometalate $Na_{14}[Zr_4(P_2W_{16}O_{59})_2(\mu_3\text{-}O)_2(OH)_2(H_2O)_4]\cdot 57H_2O$ (ZrWD 4:2) was followed by means of ^{1}H and ^{31}P NMR spectroscopy. The hydrolytic reaction proceeded with a rate constant of 8.44 (±0.36) × $10^{-5}s^{-1}$ at pD 6.4 and 50 °C, representing a 300-fold rate enhancement in comparison with the spontaneous hydrolysis of NPP (k_{obs} = 2.81 (±0.25) × 10^{-7} s^{-1}) under the same reaction conditions. The ZrWD 4:2 was also active towards hydrolysis of the more stable DNA-model substrate bis(4-nitrophenyl) phosphate (BNPP) and the RNA model substrate 2-hydroxypropyl-4-nitrophenyl phosphate (HPNP). The pD dependence profile of k_{obs} shows that the rate constants for NPP hydrolysis decrease significantly when the pD values of the reaction mixtures increase. The formation constant (K_f = 190 M^{-1}) and catalytic rate constant (k_c = 6.40 × 10^{-4} s^{-1}) for the NPP-ZrWD 4:2 complex, activation energy (E_a) of 110.15 ± 7.06 kJ mol^{-1}, enthalpy of activation ($\Delta H^{\ddagger}$) of 109.03 ± 6.86 kJ mol^{-1}, entropy of activation ($\Delta S^{\ddagger}$) of 15.20 ± 2.49 J mol^{-1} K^{-1}, and Gibbs activation energy ($\Delta G^{\ddagger}$) of 104.32 ± 6.09 kJ mol^{-1} at 37 °C were calculated from kinetic studies. The recyclability of ZrWD 4:2 was examined by adding an extra amount (5.0 mM) of NPP twice to a fully hydrolyzed mixture of 5.0 mM NPP and 1.0 mM ZrWD 4:2. The interaction between ZrWD 4:2 and the P–O bond of NPP was evidenced by a change in the ^{31}P chemical shift of the ^{31}P atom in NPP upon addition of ZrWD 4:2. Based on ^{31}P NMR experiments and the kinetic studies, a mechanism for NPP hydrolysis promoted by ZrWD 4:2 has been proposed.[1-4]



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2. Luong T. K. N., Shestakova P., Mihaylov T. T., Absillis G., Pierloot K. and Parac-Vogt T. N., *Chem. Eur. J.* 2015, **21**, 4428-4439.
3. Luong T. K. N., Absillis G., Shestakova P. and Parac-Vogt T. N., *Eur. J. Inorg. Chem.* 2014, **2014**, 5276-5284.
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Kinetic studies of phosphoester hydrolysis promoted by a dimeric tetrazirconium(IV) Wells-Dawson polyoxometalate followed by NMR spectroscopy

P14

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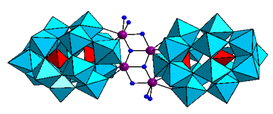
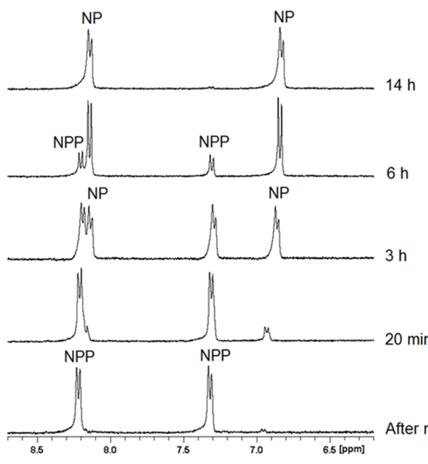
Introduction

Polyoxometalates (POMs) are oxygen anion clusters formed by early transition metals (M = V, Nb, Ta, Mo and W) in their highest oxidation state. Several classes of POMs have been reported to have potent anti-tumor, anti-viral and anti-bacterial properties, resulting in a substantial interest in the potential medicinal application of POMs. We have previously shown that a number of Zr^{IV}-substituted POM complexes could act as artificial phosphosesterases. For example, we found that a mononuclear Zr^{IV}-substituted Wells-Dawson type POM $K_{15}H[Zr(\alpha_2\text{-}P_2W_{17}O_{61})_2]\cdot 25H_2O$ accelerated the hydrolysis of the stable DNA model substrate 4-nitrophenyl phosphate (NPP), characterized by a half-life of 135 days at pH 5.0 and 50 °C, by nearly two orders of magnitude.[1] Recently, it was shown that the dinuclear Zr^{IV}-substituted Keggin type POM $(Et_2NH_2)_8[\{\alpha\text{-}PW_{11}O_{39}Zr(\mu\text{-}OH)(H_2O)\}_2]\cdot 7H_2O$ efficiently promoted hydrolysis of the extremely stable phosphodiester bis(4-nitrophenyl) phosphate (BNPP), with a 320-fold rate enhancement in comparison with pure BNPP hydrolysis.[2] In this study we explore the phosphoesterase activity of the Zr^{IV}-substituted Wells-Dawson $Na_{14}[Zr_4(P_2W_{16}O_{59})_2\ (\mu_3\text{-}O)_2(OH)_2(H_2O)_4]\cdot 57H_2O$ POM (ZrWD 4:2) that contains four Zr^{IV} centers towards NPP hydrolysis by means of ^1H and ^{31}P NMR spectroscopy. A detailed kinetic study combined with multinuclear NMR spectroscopy experiments allowed to propose the detailed mechanism[3] of NPP hydrolysis catalyzed by this POM and to obtain further insight into the role of Zr^{IV} centers in the hydrolytic reaction.[4]

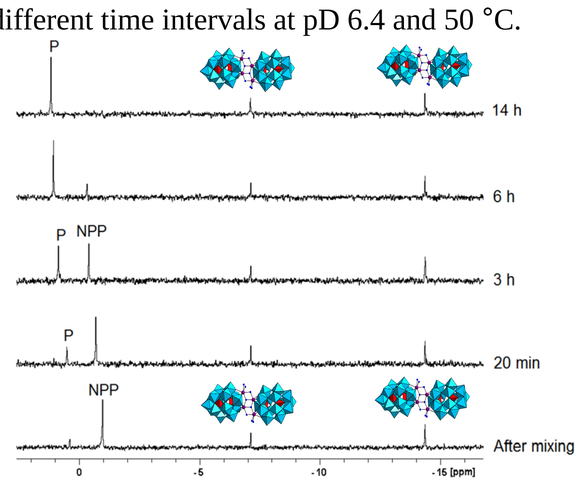
Results and discussion



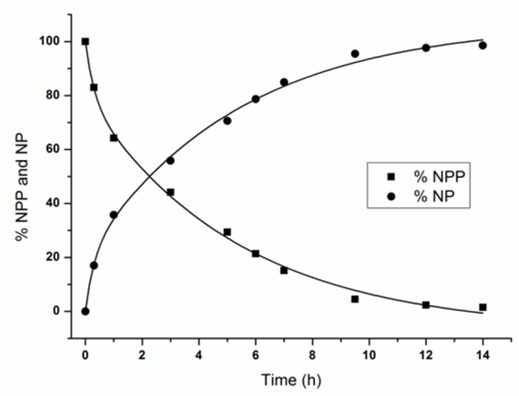
Structure of ZrWD 4:2.



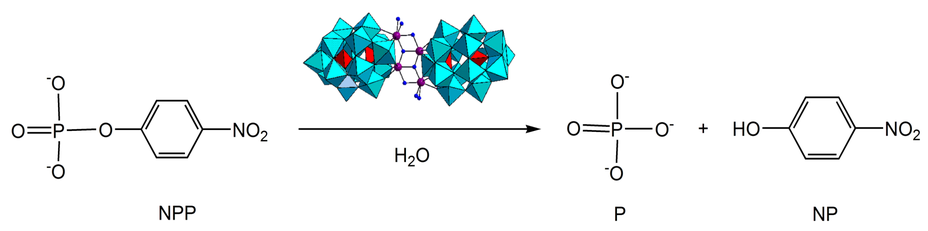
^1H spectra of 5.0 mM of NPP and 1.0 mM of ZrWD 4:2 at different time intervals at pD 6.4 and 50 °C.



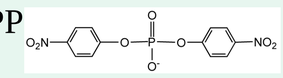
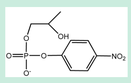
^{31}P spectra of 5.0 mM of NPP and 1.0 mM of ZrWD 4:2 at different time intervals at pD 6.4 and 50 °C.



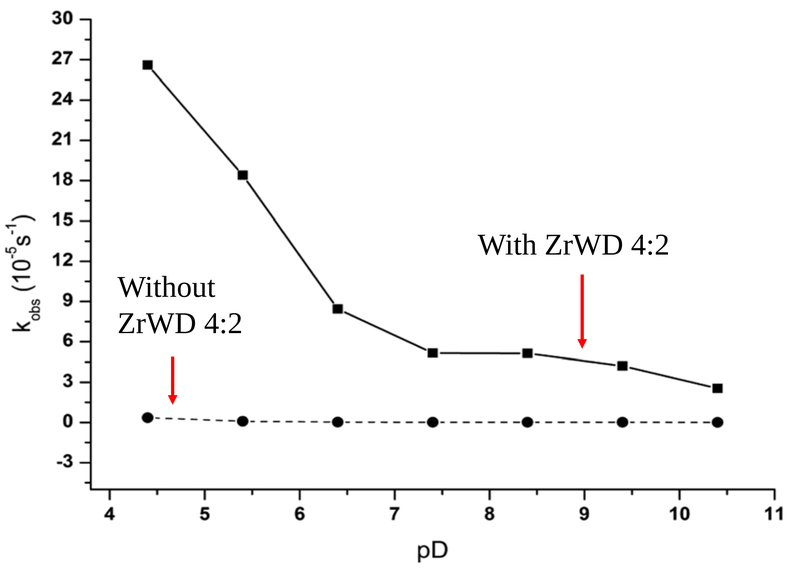
% NPP and % NP as a function of reaction time.



Hydrolysis of NPP promoted by ZrWD 4:2.

Substrate with ZrWD 4:2	k_{obs} ($10^{-7}s^{-1}$)	Rate enhancement
NPP	844 (±0.36)	300-fold
BNPP 	3.49 (± 0.22)	386-fold
HPNP 	50.6 (± 0.18)	83-fold

Effect of pD



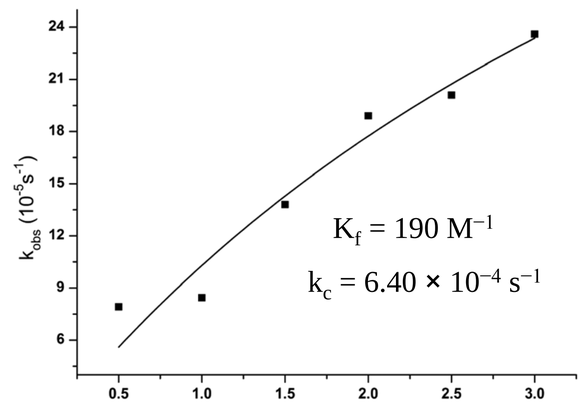
pD dependence profile of k_{obs} for the hydrolysis of 5.0 mM of NPP and 1.0 mM of ZrWD 4:2 at 50 °C.

Effect of temperature

E_a (kJ mol^{-1})	
With ZrWD 4:2	110.15 ± 7.06
Without ZrWD 4:2	147.17 ± 9.86

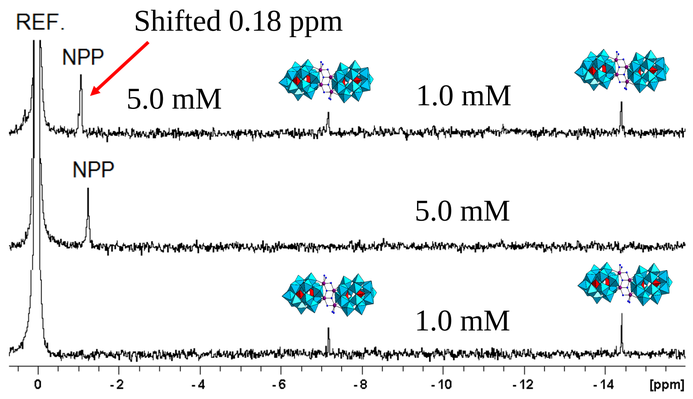
$\Delta^{\#}H$ (kJ mol^{-1})	$\Delta^{\#}S$ (J mol^{-1} K^{-1})	$\Delta^{\#}G$ (kJ mol^{-1})
109.03 ± 6.89	15.2 ± 2.49	104.32 ± 6.09

Effect of ZrWD 4:2 concentration

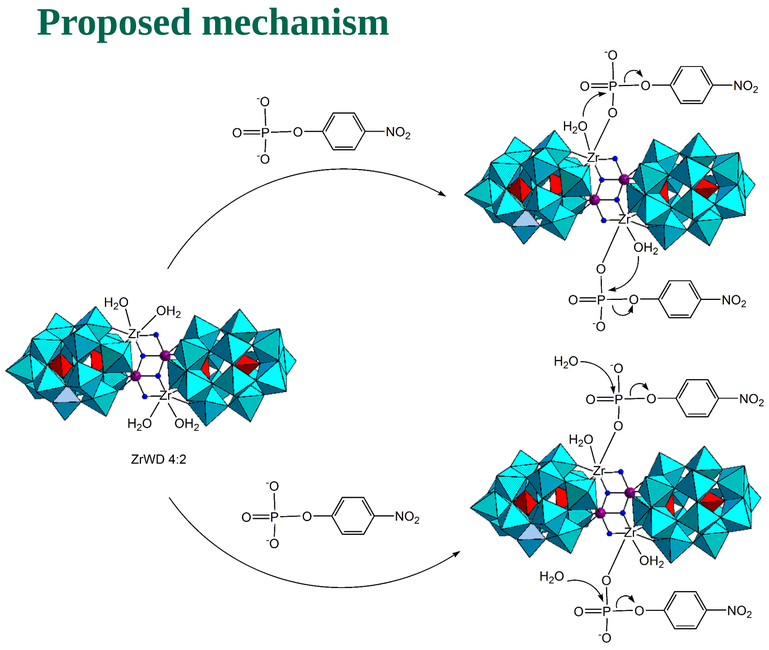


Dependence of concentration for the hydrolysis of 5.0 mM of NPP at pD 6.4 and 50 °C.

The interaction between NPP and ZrWD 4:2



Proposed mechanism



Conclusions and future work

- The presence of multiple Zr^{IV} centers is very favorable for the catalytic activity of the POM, due to the possibility of binding and activating more than one molecule of the substrate simultaneously.
- The two Zr^{IV} ions with free coordination sites are located at the opposite sites of the POM structure facilitate for the binding of two substrate molecules.
- Further exploit the hydrolytic activity of this POM towards phosphoanhydride bonds in ATP, phosphodiester bonds in DNA/RNA.

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4. T. K. N. Luong, P. Shestakova and T. N. Parac-Vogt, *Dalton Trans.*, 2016, **45**, 12174-12180

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YBMRS 2016

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YBMRS 2016

5th and 6th December 2016

Certificate of Attendance

Luong Thi Kim Nga

This is to certify the attendance and active participation to the 15th YBMRS 2016 meeting held in Spa (Belgium) from Monday 5th to Tuesday 6th of December 2016.

Spa, December 6th 2016

Prof. C. Aprile

For the Organizing Committee